Summary

A rare disease is a disease with extremely few patients, and it is estimated that there are over 7,000 rare diseases worldwide. There are many patients in Japan who suffer from symptoms that have not been diagnosed at many medical institutions and whose causes and treatments are unknown.

Following the enactment of the Act on Medical Care for Patients with Intractable Diseases in 2014, stakeholders have been diligently working to resolve challenges related to rare diseases through research and clinical projects via IRUD and public-private partnership projects such as RDCJ.

However, the 'Survey on challenges faced by patients with rare diseases (February 2023, JPMA)' [a] reported that patients still face many challenges, indicating that the path to resolving challenges in rare disease medicine is long and arduous for many stakeholders. To overcome these difficulties, it was vital to accurately understand the realities and challenges faced by healthcare professionals, who are key stakeholders supporting rare disease medical care and to identify the specific desired state and actions required for each stakeholder.

Therefore, a quantitative web survey with 327 participants and qualitative interviews with 15 participants were executed among healthcare professionals (specialists, non-specialists, genetic counselors, and nurses involved in actual clinical practice, clinical researchers (basic and applied) involved in R&D, and clinical researchers (development) to shed light on the current state of rare disease medical care from a variety of perspectives, the difficulties (sense of challenges) and their background and the expectations of stakeholders (pharmaceutical industry, academic societies, patient advocacy groups and the government).

From the perspective of each healthcare professional, we identified challenges in five areas - basic and applied research, development and clinical trials, diagnosis, treatment and prognosis management, and disease awareness. Secondary information on international cases was separately researched to compare and analyze the current state of rare disease medicine in Japan, including why these challenges are currently important in Japan. Furthermore, based on the expectations of stakeholders – the pharmaceutical industry, academic societies, patient advocacy groups and the government, we have identified the desired state, pragmatic actions, and roles required for the improvement of rare disease medicine.

As a result, five directions for resolving the challenges and actions required for each stakeholder were identified (below are the main ones). At the same time, these points also highlight areas where Japan is lagging internationally, emphasizing the need for stakeholders to fulfill their roles and collaborate to bridge the gap (details in the main document).

1. **Accelerate research and development for new modalities[1] for drug discovery and diagnostics, and building an ecosystem for this purpose**
   - [Pharmaceutical Industry & Academic Societies] Accelerating R&D through domestic and international seed[2] acquisition, cross-industry collaboration, and the creation of similar opportunities
   - [Government] Support for R&D and promoting measures for early diagnosis
   - [Patient Advocacy Group] Enhancement of organizational function, enhancement of PPI[3] through inter-organizational collaboration and dissemination of needs
   - [Government] Cutting-edge technology in drug discovery such as GMP[4]-compliant facilities and CPC[5], infrastructure support
   - [Government] Drug pricing that contributes to increasing the attractiveness of Japan's rare disease market, introduction of a pharmaceutical system and bold deregulation that contributes to the benefit of patients

[1] Novel treatments and diagnostic technologies, such as cell and gene therapy, that offer new opportunities for treatment of diseases that were previously inaccessible to treat.
[2] Fundamental research results and technologies that can be applied to the development of new drugs and research into treatment methods
[3] Patient and Public Involvement: Efforts to actively involve patients and citizens and have their opinions and needs reflected
[4] Good Manufacturing Practice
[5] Cell Processing Center: A special facility for handling, processing and culturing patients' cells, mainly in regenerative medicine and cell therapy.

2. **Improved access to medical institutions and professionals that can provide testing, diagnosis and treatment as well as information on pharmaceuticals and products in development**
   - [Academic Societies / Government] Consolidation and networking of functions between medical institutions and healthcare professionals to speed up testing
   - [Pharmaceutical industry / Academic Societies / Patient Advocacy Groups / Government] Ensuring the quality and strengthening standardization and dissemination of information related to testing, treatment, medicines and clinical trials
   - [Government] Establishment of a data infrastructure and system to promote cooperation between medical institutions and improve the efficiency of information transmission
   - [Government / Patient Advocacy Groups] Improving the functionality of the entire medical system related to rare diseases through legislation, establishment of registries[6] and promotion

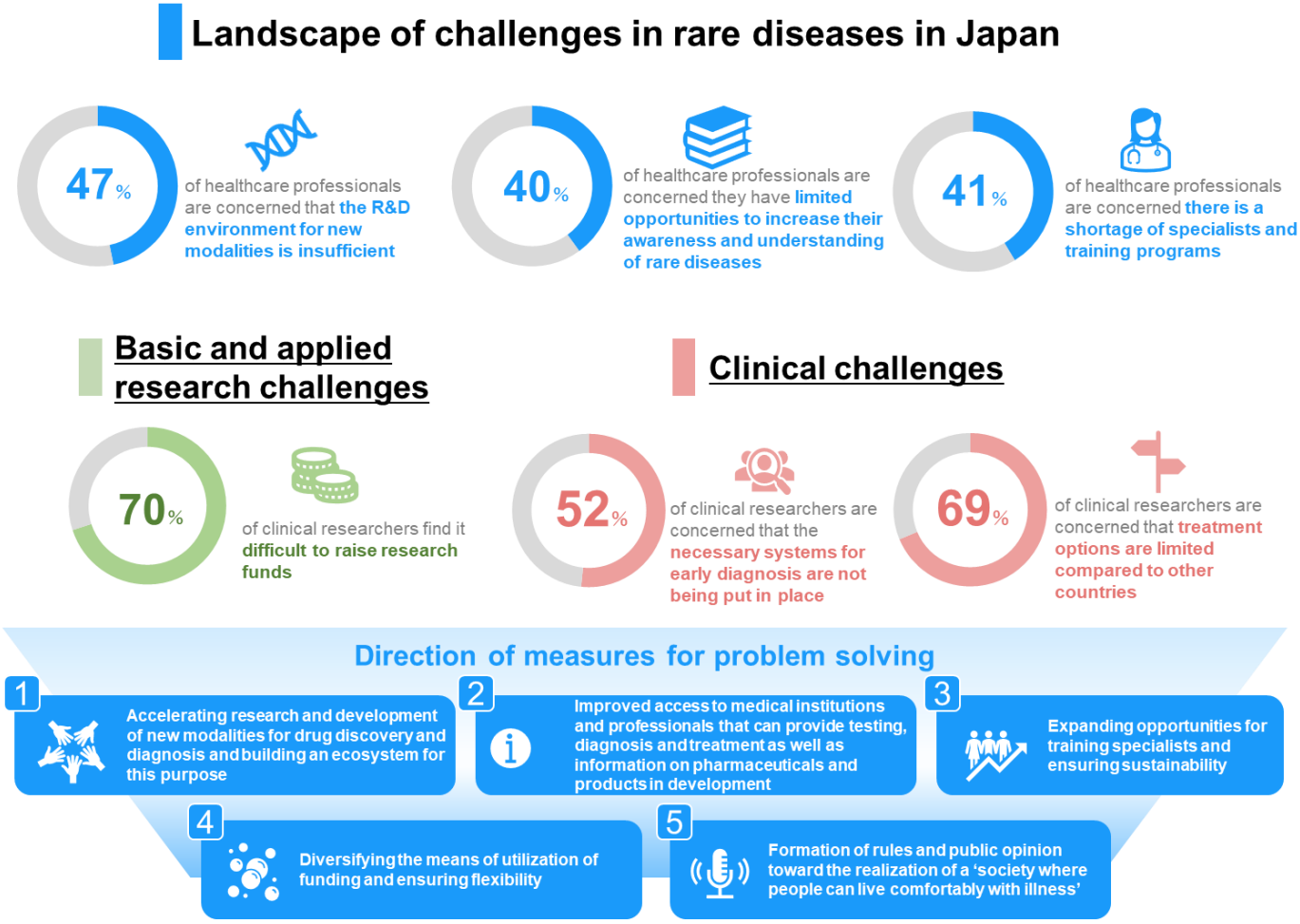
3. **Expanding opportunities for training specialists and ensuring sustainability**
   - [Government] Eligibility for medical fees related to rare disease medical care and expanding incentives
   - [Academic Societies / Government] Creating an attractive career development environment, sharing role models, success stories and minimizing barriers to participation
   - [Academic Societies / Government] Establishment of programs in specialized education courses and accelerating the mobility of human resources
   - [Government] Strengthening literacy among government personnel involved in drug development, medical welfare and reducing disparities

4. **Diversifying the means of utilization of funds and ensuring flexibility**
   - [Government] Hiring personnel, increasing the budget required for infrastructure development, ensuring flexibility in certification requirements for research funds, expanding the scope of targets and accelerating the attraction of private funds
   - [Patient Advocacy Groups] Diversifying activities and expanding fundraising methods through dissemination and strengthening organizational functions

5. **Formation of rules and public opinion toward the realization of a 'society where people can live comfortably with illness'**
   - [Government] Policy discussions aimed at reducing the burden on patients and families (introduction of intractable and rare diseases in the primary education course, introduction of special measures in research and development and clinical practice, etc.)
   - [Pharmaceutical industry / Academic Societies / Patient Advocacy Groups] Communicating the necessity and value of rare disease medical care and drug discovery in Japan

[6] A database that collects and manages medical data on patients with a disease.

Figure S-1: Landscape of challenges for healthcare professionals and the direction of measures



1. Background and purpose of the survey

The ‘Survey on challenges faced by patients with rare diseases (February 2023, JPMA)’ [a] once again highlighted the fact that many challenges remain unresolved for patients and their families affected by rare diseases, making it necessary to hear the voices of healthcare professionals supporting rare disease medical care in Japan and implement concrete initiatives.

IRUD, RDCJ and JPMA planned this survey with the aim of ‘contributing to improve the quality of medical care and research related to intractable and rare diseases by identifying challenges faced by healthcare professionals involved in rare diseases and proposing and implementing solutions, thereby contributing to patients and their families.’

In planning and promoting this survey, we utilized the IRUD and RDCJ healthcare professional networks, requested a quantitative survey (online questionnaire) from approximately 1,000 people (healthcare professionals belonging to the IRUD Diagnostic Committee, healthcare professionals introduced by the committee and healthcare professionals participating in the RDCJ) and received responses from 327 people. Additionally, we received cooperation from a total of 15 healthcare professionals who participated in the qualitative survey (interviews).

To ensure neutrality and objectivity, this survey was executed with the planning and operational support of a third-party organization (EY Strategy & Consulting Co., Ltd.).

2. Definition of rare diseases

A rare disease refers to a disease with an extremely small number of patients, and it is said that there are more than 7,000 rare diseases in the world [b]. Because of the small number of patients, it is difficult for patients' voices and needs to be heard, which leads to delays in R&D and insufficient care in actual clinical practice. The United States, Europe and Japan each have different definitions for designating a rare or intractable disease, and they are defined mainly in terms of patient population, severity of the disease, business viability, unmet needs, efficacy and safety (Figure 2-1).

Figure 2-1:

Definitions of rare and designated intractable diseases in each country (underlying laws and regulations) [c], [d], [e], [f]

Classification	US (Orphan Drug Act)	Europe (EC No. 141)	Japan	
			Rare diseases (Pharmaceutical and Medical Device Act)	Designated intractable disease (Intractable Diseases Act)
Patient population	▸ The number of patients is less than 200,000 (equivalent to approximately 0.06% of the total population)	▸ The number of patients is less than 0.05% of the total population (equivalent to approximately 220,000 people)	▸ The number of patients in Japan is less than 50,000 (equivalent to approximately 0.04% of the total population)	▸ The number of patients in Japan is less than 0.01% of the total population (equivalent to approximately 120,000 people)
Severity of disease	N/A	▸ Even if the morbidity condition is not met, a drug may be designated if it is indicated for treating a life-threatening, severely debilitating or severe chronic disease	▸ A drug or medical device indicated for treatment of severe diseases, including diseases that are difficult to treat	▸ Diseases that require long term treatment
Business potential	▸ Even if the incidence rate condition is not met, a product may be subject to designation if it is expected that R&D costs will not be recovered through sales in the United States	▸ A drug may be designated if it is a rare disease treatment drug with no prospect of recovery from investment	N/A	N/A
Unmet needs	N/A	▸ There are no satisfactory EMA-approved alternatives or there is a significant benefit to patients with the disease	▸ It is a drug or medical device that is highly necessary for medical purposes ▸ No suitable medicine, medical device or treatment	▸ The mechanism of disease onset is unclear ▸ There is no established treatment
Efficacy/safety	N/A		▸ Expected to be more effective or safer than existing products ▸ It is a drug or medical device that has a theoretical basis for use in the target disease and has an appropriate development	N/A

3. Approach

To identify the challenges faced by healthcare professionals from a more multifaceted perspective, this survey requested responses from healthcare professionals involved in rare disease care in multiple occupations (including concurrent positions) in R&D and clinical practice (Figure 3-1).

The quantitative survey targeted healthcare professionals belonging to the IRUD Diagnostic Committee, healthcare professionals referred by the committee and healthcare professionals participating in the RDCJ.

In the qualitative survey (Figure 3-2), the survey was executed on those who offered to cooperate and could arrange the schedule among the participants of the quantitative survey, with priority given to having as many healthcare professionals participate as possible. Therefore, there is some bias in the attributes of the survey subjects (age, gender, position, medical department, type of facility, amount of experience, etc.), and healthcare professionals with relatively little involvement in rare diseases are not included. In the [Main Section], the results and opinions related to the main points of discussion are described and all survey results including other detailed data are published in the attached [Reference Section].

Figure 3-1: Approach overview

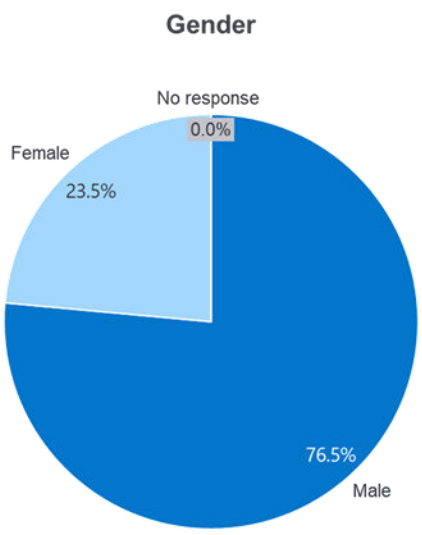
Classification	Quantitative (web survey) research	Qualitative (interview) research
Purpose	▸Quantitatively identify the current status, challenges, and future expectations of rare disease medical care	▸Identify context and reality of quantitative survey responses
Region	▸Nationwide	
Duration	▸25th July 2024 to 23rd August 2024	▸2nd September 2024 to 13th September 2024
Target person (job type)	▸Clinical physicians: specialists and non-specialists ▸R&D: clinical researchers (basic and applied), clinical researchers (development)* ▸Other HCPs** (genetic counselors, nurses) *Doctors involved in clinical trials **Healthcare Professionals	
Recruitment method	▸Approximately 1,000 medical professionals, including those who belong to the IRUD Diagnostic Committee, those who have been introduced by the committee, and those who participate in the RDCJ	▸Those who agreed to participate out of the 327 people who participated in the quantitative survey
Number of valid responses	▸327	▸15
Analysis assumptions and constraints	▸In accordance with the recruitment method, some attributes (age, gender, position, medical department, etc., explained in detail in the main text) are biased ▸Responses by job type include multiple responses (concurrent positions)	
Inspection Agency	▸EY Strategy & Consulting Co., Ltd. ▸Social Survey Research Information Co., Ltd.	

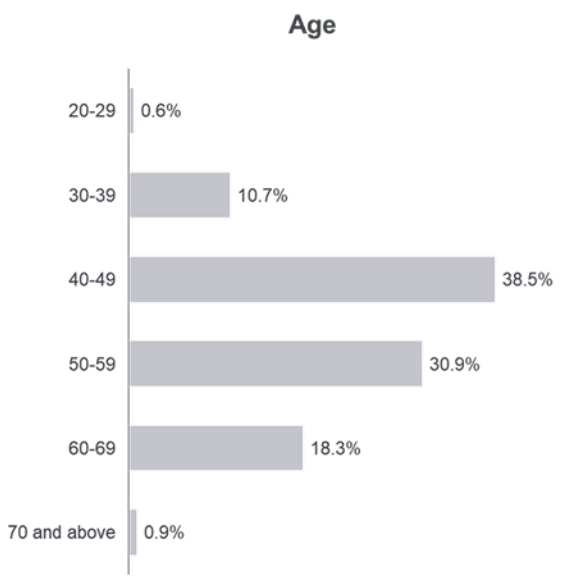
Figure 3-2: Details of qualitative interviewees

	#	Occupation/activity ratio (total 10)						Facility Attributes				Experience		
		Clinician (specialist)	Clinician (non-specialist)	Clinical researcher (basic and applied)	Clinical researcher (Development)	Other HCPs	Clinical researcher – Details*	Facility type	Region	Department/Disease area	Professional staff Yes/No	Years involved	Consulted by [Person]	Consulted [Person]
Specialist	1-1	3	2	2	2	2	n/a	University Hospital	Kansai	Paediatrics	Full-time	10~	20	10
	1-2	3	4	1	0	2	n/a	National and public hospitals (other than university hospitals)	Chubu/Hokuriku	Paediatrics	Full-time	~3	5	30
	1-3	4	0	6	0	0	n/a	University Hospital	Tokyo Metropolitan Area/South Kanto	Collagen Disease	No	10~	30	5
Non-specialist	2-1	1	8	0	0	1	n/a	Hospitals and Clinics	Tokyo Metropolitan Area/South Kanto	Neurology	Full-time	10~	15	5
	2-2	3	4	2	1	0	Basic, Applied (Non-clinical), Clinical/Clinical Trials, TR	University Hospital	Northern Kanto/Koshinetsu	Paediatrics	Full-time	10~	10	0
	2-3	1	8	1	0	0	n/a	University Hospital	Tokyo Metropolitan Area/South Kanto	Paediatrics	Full-time	3~10	10	20
Clinical researcher (basic and applied)	3-1	0.5	0.5	5	4	0	Basic, Applied (Non-clinical), Clinical/Clinical Trials, TR	National and public hospitals (other than university hospitals)	Tokyo Metropolitan Area/South Kanto	Neuromuscular disease	Full-time	10~	0	0
	3-2	2	0	5	2	1	Basics, Applications (Non-clinical), TR	University Hospital	Chubu/Hokuriku	Other general hereditary disease	No	10~	0	0
	3-3	4	0	6	0	0	Basic, applied (non-clinical), clinical/trial	University Hospital	Tokyo Metropolitan Area/South Kanto	Paediatric diseases	Full-time	10~	10	10
Clinical researcher (development)	4-1	5	0	1	4	0	Basic, clinical trials, TR	University Hospital	Chugoku and Shikoku	Neuromuscular disease	Full-time	10~	30	20
	4-2	8	0	1	1	0	Clinical trials	National and public hospitals (other than university hospitals)	Kansai	Endocrinology and Metabolic Disease	Full-time	10~	100	10
	4-3	5	1	3	1	0	Basic, clinical and experimental	University Hospital	Chugoku and Shikoku	Immunodeficiency disease	Full-time	10~	10	5
	4-4	0	0	0	5 IRUD Clinical Researcher	5 Genetic Counsellor	Clinical trials	University Hospital	Kansai	All other hereditary disease	Full-time	3~10	0	0
Other HCPs	5-1	Genetic counselors: 8, Nurses/midwives: 2					n/a	University Hospital	Chugoku and Shikoku	Department of Clinical Genetics and Gene Therapy	Full-time	10~	0	0
	5-2	Genetic counselor: 10					n/a	University Hospital	Kyushu	Department of Clinical Genetics and Gene Therapy	Full-time	10~	0	0

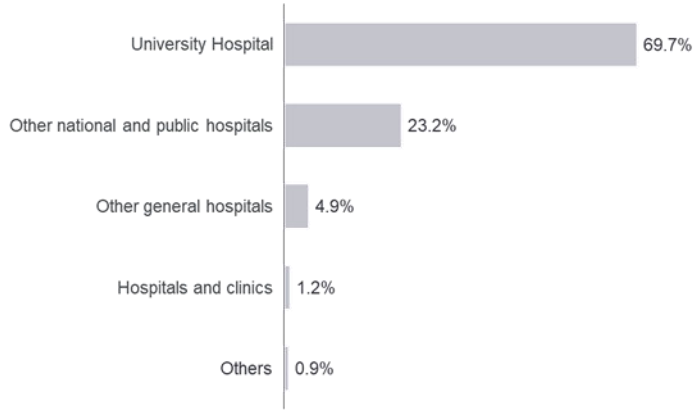
*TR (Translational research): A field of medical research that considers the process from non-clinical research to clinical development as a continuum, aiming for a smooth transition from basic research to clinical application.

Respondent attributes

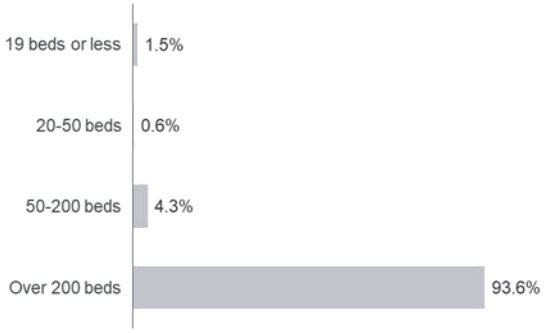




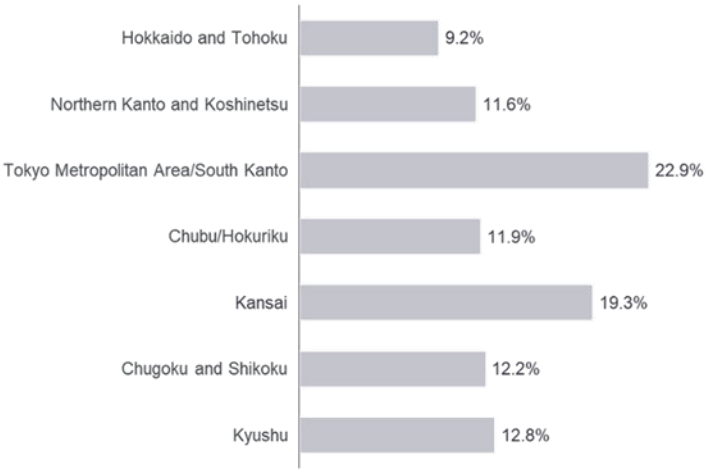
Type of facility



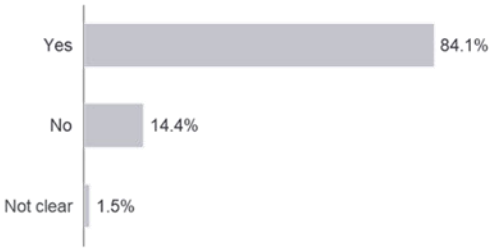
Number of hospital beds at affiliated facilities



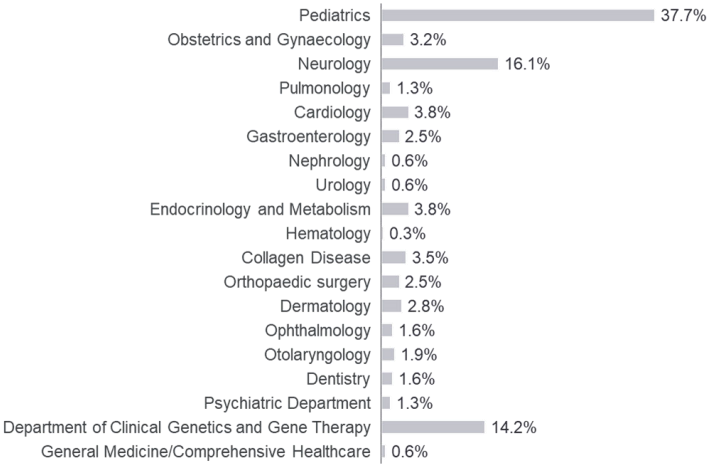
Region/area of affiliated facility



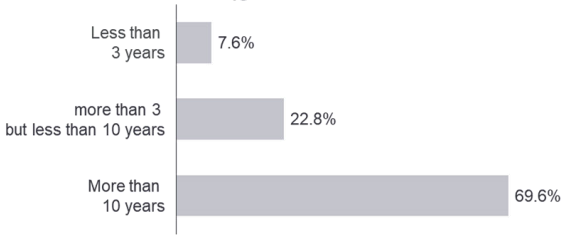
Availability of specialized staff at affiliated facilities



Departments Specialists, non-specialists, other HCPs (genetic counselors, nurses)



Years of experience in rare disease treatment for support specialists, non-specialists, and other HCPs (genetic counselors and nurses)



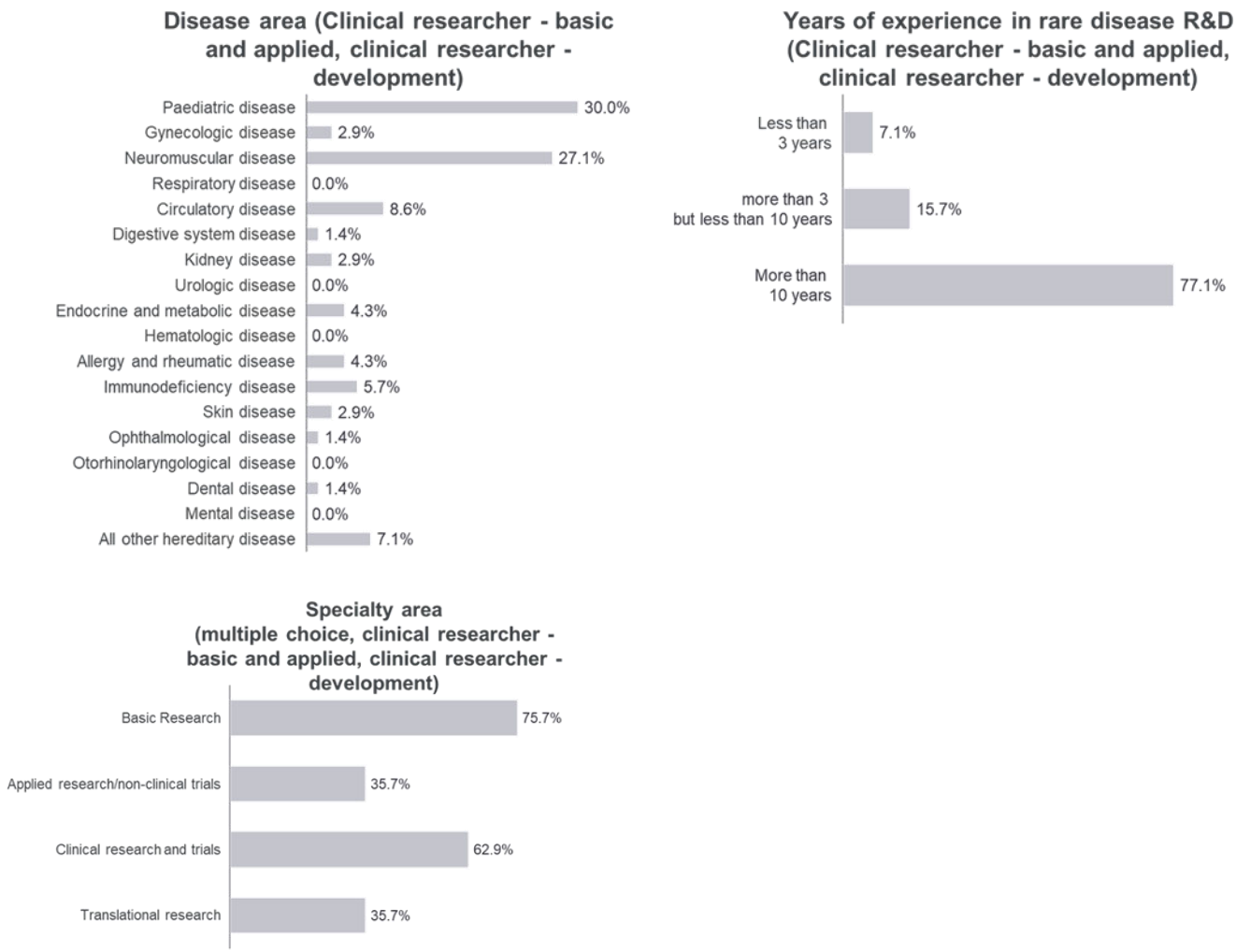
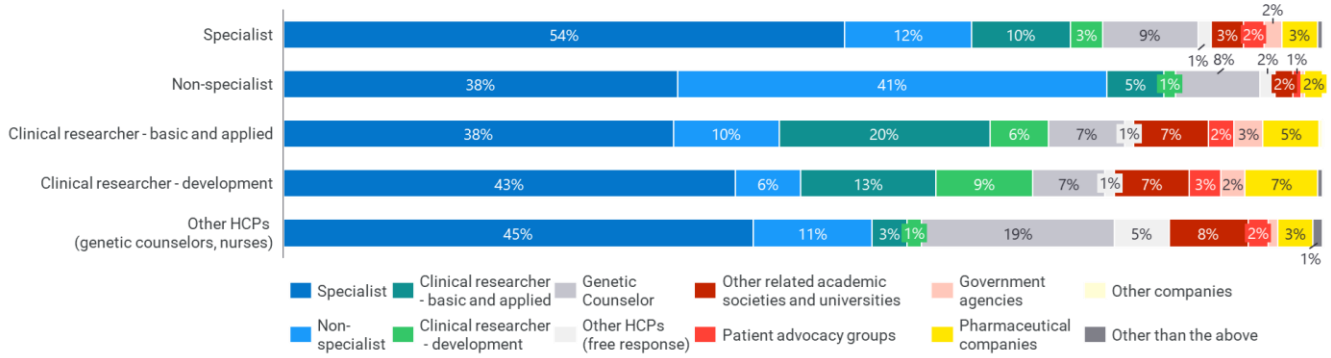


Figure 3-3: Percentage of people with experience of collaboration with other healthcare professionals and stakeholders



■Survey: Web survey
■Question: Regarding your activities related to rare diseases in the past year, have you collaborated with others? Please answer with an integer between 0 and 10 so that the total for the people you collaborated with is 100%.
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)

Attitude and motivation to participate in activities related to rare diseases

This survey confirmed the attitude and motivation for involvement in activities related to rare diseases (Figure 3-4). Many healthcare professionals place top priority on contributing to patients despite their busy schedules, but at the same time, there are many situations where they have no choice but to participate in activities on a semi-volunteer basis in addition to their daily work, and they are involved in situations without clear rules or incentives.

To improve rare disease medical care, it is necessary to create an environment in which healthcare professionals can continuously focus on activities related to rare diseases and contribute to patients and their families.

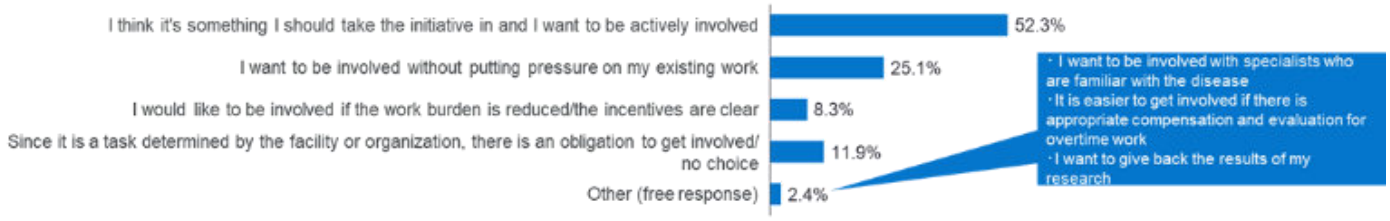
"Research into rare diseases is very labor intensive, and the work is diverse and burdensome. I want to get involved, but the total workload is too much, and I am struggling. If I could get support from my department, I would be able to concentrate more on rare disease activities.
(Specialist / Collagen Disease Department)

"Naturally, I would like to be actively involved, and my motivation is not the pursuit of profit, but the search for a future understanding and solution for rare diseases.
(Clinical researcher (Basic and applied) / Other hereditary diseases)

"In Japanese society, we tend to expect people to do things with good intentions, and there is a trend to expect researchers to donate their time and abilities for free. This will not increase the number of people who join us. Isn't it better to be able to pursue fulfillment based on the premise that people receive compensation for their work?
(Clinical researcher (Basic and applied) / neuromuscular disease)

"Although we feel the need to be proactive in solving patients' problems, we are troubled by the discrepancy between our own motivation and what we are able to do as this puts a strain on our daily work.
(Genetic Counselor / Clinical Genetics)

Figure 3-4: Attitude and motivation towards activities related to rare diseases – Top selection result



■Survey: Web survey
■Question: Please choose the top three that apply to you regarding your attitude and motivation for participating in activities related to rare diseases (ranking format)
■Subjects: 327 specialists, non-specialists, clinical researchers (basic and applied), clinical researchers (development) and other HCPs (genetic counselors and nurses)